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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,517	EATON ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *112505*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 are pending in the instant application and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 25 November 2005 have been fully considered but are not deemed persuasive.

Specification

Applicant's submission of a marked-up copy of the substitute specification is noted. This completes the requirements for filing a substitute specification. The previously filed clean copy of the substitute specification has been approved for entry.

Claim Rejections - 35 USC §§ 101/112

Claims 1-5 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons of record in the previous Office action and for those reasons provided below.

Applicant argues (page 3 of the response) that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is

"currently available" to the public in order to satisfy utility requirements. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." For reasons discussed in the previous Office action, even if the encoding polynucleotide has utility, one cannot on that basis alone support a utility for the encoded protein and antibody which binds it because the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable. For example, Haynes et al. (Electrophoresis 19 : 1862-1871 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1). Haynes et al. provide evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (page 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. The results of Hu et al., J. Proteome Res. 2003, were discussed in the previous Office

action and show that the correspondence between mRNA and protein levels cannot be assumed in cancerous tissue.

Applicant argues on pages 4 and 27 that *In re Brana* states that "Usefulness in patent law... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to administer to humans;" and that the USPTO has the initial burden of showing "that one of ordinary skill in the art would reasonably doubt the asserted utility." The argument has been fully considered, but is not persuasive. While *Brana* did deal with a rejection under 35 USC 112, first paragraph, the rejection was directed toward utility—specific, substantial and credible use—instead of enablement. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement, one must know how to use the invention without undue experimentation. In the instant situation, Applicant claims an antibody which binds to the polypeptide of SEQ ID NO:12. The USPTO has met the burden of showing one skilled in the art would reasonably doubt the asserted utility by showing that the correspondence between mRNA and protein levels is not predictable and will be further discussed below.

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is an antibody which binds a polypeptide encoded by a nucleic acid with no known specific association other

than that asserted by Applicant of higher expression in normal lung compared to lung tumor. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in lung tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. Proteins not identical to SEQ ID NO:12 have not been shown to exist in nature, let alone in lung tissue. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none of those identified as a tumor marker were identical or highly similar to SEQ ID NO:12. Therefore, the connection of SEQ ID NO:12 to tumors was not known and there is no prior art of record to help elucidate an enabling (or specific and substantial) use for PRO300. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not predictable. There is very little guidance or direction about using the claimed antibodies except that the encoded nucleic acid of SEQ ID NO:11 is more highly expressed in normal lung compared to lung tumor. The

specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons, it would require undue experimentation to use the invention as claimed.

On page 5-6, Applicant cites *Fujikawa v. Wattanasin,*, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well-established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in nucleic acid expression of PRO300 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

Applicant argues (pages 7-8) that one skilled in the art would be convinced there is a "reasonably probability" that the expression of the polypeptide will correlate with encoding nucleic acid expression or, put another way, one skilled in the art would not reasonably doubt the correlation. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "reasonable probability" that mRNA and protein levels will correlate for a given protein, there is influential prior art of record that requires

the Examiner maintain that, as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12. The advent of proteome analysis has only recently begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. It is also noted that the information on which the assumption of a correlation between mRNA and protein levels was based came from findings in normal, noncancerous tissue. Indeed, there is evidence in the art to refute generalizations about gene/protein correlations even in normal tissue. For example, Haynes et al. (Electrophoresis 19 : 1862-1871,1998) as discussed above showed from studies with yeast that among 80 proteins studied which were relatively homogenous in half-life and expression level, no strong correlation existed between protein and transcript levels. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph, and Figure 1). In a separate comparison by Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002) examining lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) it is stated, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other

systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Chen et al. (Mol. Cell Proteomics 1.4:304, 2002) studied 165 proteins from lung adenocarcinoa tumors expressed by 98 individual genes Their findings provide further evidence that one cannot assume the level of mRNA will correlate with the level of expressed protein for any given gene or any given protein (paragraph bridging pages 312-313):

> The results of this study indicate that the level of protein abundance in lung adenocarcinomas is associated with the corresponding levels of mRNA in 17% (28 proteins) of the total 165 protein spots examined. This was substantially higher than the amount predicated to result from chance alone (which was 5.1) and suggest that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas. We also demonstrated that the expression of individual isoforms of the same protein may or may not correlate with the mRNA, indicated that the separate and likely post-translational mechanisms account for the regulation of isoform abundance. These mechanisms may also account for the differences in the correlation coefficients observed between stage I and stage III tumors, indicating that specific protein isoforms show regulatory changes during tumor progression.

Further it was shown (page 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in

levels of expression with their encoded proteins. Given the unknown amount that mRNA copy number of PRO300 increased in normal tissue compared to tumors, and the evidence provided by Haynes et al., Hu et al., Fessler et al. and Chen et al., one skilled in the art would not have assumed that a small increase in mRNA copy number would correlate with significantly increased polypeptide levels. The level of increase of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO300 polypeptide levels were significantly increased significantly in normal lung compared to the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility. As stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level

range for normal and tumor tissues, the specification has not provided the invention in a form that can be used without necessary further experimentation.

At pages 8-9 of the response, Applicant argues that Example 18 of the specification establishes a utility for the claimed invention because the gene encoding the PRO300 polypeptide "is differentially expressed in lung cancers compared to normal lung tissue". Applicant further refers to the Declaration of Grimaldi (submitted Jan. 3, 2005) as demonstrating "at least a two-fold difference between normal and tumor samples" and that "the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes". Applicant's arguments and the Declaration have been carefully considered, but are not found to be persuasive. Example 18 does not provide any information as to the expression levels of the encoded protein. Declarant is making a conclusion which is not based on any evidence of record regarding the encoded polypeptide. As pointed out above, the art of record clearly establishes the fact that protein expression levels are not predictably correlated to mRNA expression levels. Therefore, one cannot conclude based on mRNA data alone what the protein expression pattern for a given protein will be. Because there is no evidence to demonstrate that the encoded polypeptide is differentially expressed in lung tumor, then utility has not been established for the encoded polypeptide as a diagnostic marker and no utility has been established for the antibody that binds to the encoded protein as a diagnostic marker.

Applicant argues at page 10 of the response that "Examiner rejects Dr. Grimaldi's assertion that data from pooled samples are more likely to be accurate

than data from a single individual". However, the Examiner never rejected the assertion. The statement of Dr. Grimaldi is "Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." The corollary to this statement would be that data obtained from a single individual is more likely to be *inaccurate.* This being the case, one of skill in the art would question whether tissue from an individual could be assed for whether or not it is cancerous. If the skilled artisan is using the claimed invention to diagnose cancer, they will not be using pooled samples – they will be looking at an individual. If this information is more likely to be inaccurate, then it is not predictive that it would be useful for this purpose. Applicant states that the gene expression studies were made from pooled samples, and that this clearly indicates that multiple tumors were tested. This argument is not persuasive. Actually, this means that multiple samples were included in the pool, but it is not clear that multiple tumor types were sampled and it clearly does not provide any information as to what types of lung tumors were included. Applicant is asserting that the claimed antibodies would be useful for discriminating between normal lung and lung tumor. However, different types of lung tumors exhibit different patterns of gene expression. Lung tumors in different stages of cancer can exhibit different patterns of gene expression as well as various types of lung cancer. The specification fails to identify what types of "lung tumor" was used in generating the gene expression data. This is important because one lung tumor may express the protein while other types do not – the conclusion in the instant specification indicates that pooled lung tumor tissue expresses PRO300 gene at

a lower level than normal lung. However, were PRO300 differentially expressed and were this expression significant, repeatable and the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities. There is no showing or reasonable expectation that PRO300 is differentially expressed in certain cancers, even though its encoding nucleic acid of SEQ ID NO:11 appears to be more highly expressed in normal lung compared to "lung tumor", though specifically which kind and at what levels is unknown.

At page 10 of the response, Applicant refers to the PTO Utility Examination Guidelines regarding the opinion of qualified experts. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). 1) In the instant case, the nature of the fact sought to be established is whether or not Example 18 of the instant specification supports the asserted utility of the claimed antibodies as a diagnostic tool for lung cancer. The Declaration of Grimaldi does not teach the level of reproducibility or the level of reliability of the results of Example 18. There are no relative or absolute levels of PR0300 mRNA in control or tumor tissue disclosed. Neither

the specification nor the declaration provides any evidence that indicates what the differences were or if they were statistically significant. If a clinician took a lung tissue sample from a patient with lung cancer, for example, what is the likelihood that when compared with normal tissue, the level of PR0300 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Applicant has provided no indication of the nature or number of samples that were used. The only thing Applicant teaches is that PR0300 mRNA was "overexpressed", and this does not enable the skilled artisan to differentiate between expression levels in order to diagnose any diseases. Furthermore, the is absolutely no information regarding protein expression levels and the prior art teaches that protein expression cannot be predicted from gene expression levels (see arguments to follow). 2) Regarding the strength of opposing evidence, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (for example, see Hu et al., of record). Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. Saito-Hisaminato et al (DNA Res., 9:35, 2002) demonstrate that among 23,040 genes studied in normal human tissue, 4080 genes were highly expressed (greater than 5- fold higher than in other tissues) in one, or only a few tissues (see abstract, lines 3-5). This represents about 18% of the total genes tested.

Saito-Hisaminato et al. only disclose genes that are highly expressed in one tissue compared to other tissues (i.e. greater than 5-fold difference). A 5-fold difference is greater than the difference required to establish that a gene is "overexpressed" or "differentially expressed" by comparison in the specification. In the instant application, there are no relative or absolute expression levels. Thus, Hu et al. and Saito-Hisaminato et al. constitute strong opposing evidence. 3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Grimaldi is employed by the assignee and is an inventor in this application. 4) Finally, with regard to the presence or absence of factual support for the expert's opinion, it is noted that while the declaration of Dr. Grimaldi does not discuss the specific PRO300 of the instant application, no data is disclosed, and percentage increases or levels of significance are not disclosed. Dr. Grimaldi states that because the technique used in the specification relies on the visual detection of ethidium bromide staining on agarose gels, "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA". This statement is not supported by any facts or evidence of record, making it difficult for the Examiner independently to draw conclusions. Based on a consideration of the totality of the evidence, it is proper to maintain the rejections.

At page 11 of the response Applicant states "they are not asserting that the claimed antibodies will provide a definitive diagnosis of cancer, but rather that they are useful alone or in combination with other diagnostic tools to assist in the diagnosis of lung cancer". Applicant's argument has been carefully considered,

but not deemed persuasive. For an antibody to be useful in the diagnosis of cancer, there must be a correlation or nexus between the antibody (or the protein to which it binds) and the cancer to be detected. The instant specification provides information regarding the cDNA encoding PRO300 and its presence in lung tissue. There is no information in the instant specification regarding PRO300 protein expression in lung tissue. Therefore, there is no established nexus between PRO300 protein and lung cancer. Applicant has argued that mRNA expression levels are predictive of protein expression levels. This argument is not persuasive in view of the prior art of record and the arguments above and below.

Applicant's arguments at pages 12-13 regarding aneuploidy are noted. Applicant's assertion that Hittelman et al. does not discuss mRNA is persuasive.

Applicant argues (pages 13-14) that the declarations of Grimaldi (second declaration) and Polakis support the teachings in Molecular Biology of the Cell, Genes VI, and Zhigang et al. (2004), that it is generally accepted that mRNA and protein expression are positively correlated. The argument has been fully considered, but is not persuasive. As discussed above and in the previous Office action, there is sound supporting evidence showing the unpredictability of saying level of expression of a particular nucleic acid will correlate with expression of the encoded protein. The argument of correlation between nucleic acid and protein expression has been previously addressed. Zhigang find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker.

There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application, we have *no* correlation and the claimed invention is not PSCA. There is no suggestion of multiple tumors tested. There are [0530] just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed previously, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO300 nucleic acid and/or protein. If Zhigang et al. had obtained only a 5% correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Applicant asserts at page 16 that the Examiner has not fully considered and responded to the previously filed arguments and the Zhigang reference. Applicant cited Zhigang to support the position that it is a "general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein" (page 16 of previous response). Zhigang et al. studied the expression of a single gene, PSCA. Zhigang did not extrapolate the results of PSCA to expression of mRNA and proteins in general. Further, one of ordinary skill in the art would not view the results of Zhigang et al. as predictive of all genes and protein expression because Zhigang et al. is but a single data point (i.e. examined only a single gene). The Examiner has never asserted that mRNA expression never correlates with protein expression, however, the art is replete with studies which demonostrate that mRNA expression does not reliably

correlate with protein expression. The art is silent on predicting when the expression of a protein will correlate with mRNA expression and in view of the art of record, one of ordinary skill in the art would not reasonably assume such in the absence of evidence.

Applicant argues (page 16) that the Meric et al. (Mol. Cancer Ther., 2002) reference was also not considered or responded to. Applicant cited Meric et al. and quoted

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells ... [M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. (page 971)

Applicant then concludes that "[t]hose of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression". Applicant's argument has been considered, but Applicant's conclusion is not supported by the evidence of Meric et al. A full reading of Meric et al. demonstrates that the goal of the review was to examine how translation initiation was related to cancer. Meric et al. state that several alterations in translational control occur in cancer, that variant mRNA sequences can alter the translational efficiency of individual mRNA molecules and changes in the expression or availability of components of the translational machinery and in the activation of translation can lead to more global changes in protein synthesis (see abstract and page 973, column 2, paragraph 2)). Therefore, Meric et al. support the position that mRNA levels are not predictive of protein levels because there are a

number of variables involved at the translation stage that could alter the amount of protein being produced from a given mRNA. Those of skill in the art would be focusing on differences in gene expression between cancer cells and normal cells *regardless* of protein expression levels, because if the differences are significant, they could provide to be useful for diagnostic and potentially, therapeutic purposes. But to conclude that the skilled artisan would not be looking at differences in gene expression if the protein expression did not correlate is not supported by any facts or evidence of record. Meric et al. does not teach anything about the claimed invention. Meric et al. does not teach that mRNA expression levels are predictive of protein expression levels. Meric et al. provides evidence that protein expression levels are regulated at the translational level, and such regulation can be altered by a number of factors. Therefore, it would be fair to conclude that the art of Meric et al. supports the position that mRNA expression levels are not predicative of protein expression levels.

Applicant argues (pages 17-18) that the report of Haynes et al. and Gygi et al. (Mol. Cell. Biol., 1999) do not support the Examiner's position that mRNA levels do not correlate with protein levels, pointing out that Haynes did not look at *single* genes and corresponding protein level but instead looked at a group of genes. The argument has been fully considered, but is not persuasive. A complete reading of Haynes and Gygi et al. continues to support the reliance on Haynes et al. Applicants' point to the correlation coefficient of 0.935 in Haynes et al., saying that this shows a correlation instead of the lack of one. However, a full reading of Haynes et al. clarifies the data (page 1726, first full paragraph):

> For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data set (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was 0.356. (emphasis added by Examiner)

Contrary to Applicants' assertion that Gygi et al.support the correlation of mRNA and protein levels, Gygi et al. show in Figure 5 the same figure as Fig. 1 of Haynes and show in Fig. 6, what is described for the Pearson correlation coefficients in the cited paragraph above. Gygi et al. say beginning in the last sentence in col. 1 of page 1727 that, "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al. and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively). Therefore, contrary to Applicant's assertion,

Haynes et al. and Gygi et al. did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO300 nucleic acid was isolated).

Applicant argues at Haynes and Gygi looked at static levels of mRNA across different genes and not changes in the level of expression for a single gene. Applicant asserts that changes in mRNA level for an individual gene are generally correlated with changes in the level of the encoded protein (see page 19 of response). Applicant's argument has been carefully considered, but is not found persuasive. Applicant has provided no evidence to support such a conclusion. The art of record demonstrates that mRNA levels of expression are not predictive of protein levels of expression (see at least Haynes and Gygi above). The art of record, Meric et al., demonstrates that protein translation is affected by a number of variables, and these variables are clearly in play in cancer. Meric et al. state that several alterations in translational control occur in cancer, that variant mRNA sequences can alter the translational efficiency of individual mRNA molecules and changes in the expression or availability of components of the translational machinery and in the activation of translation can lead to more global changes in protein synthesis. Because changes in protein translation occur in cancer which affect protein expression levels and because mRNA and protein levels do not predictably correlate, Applicant's conclusion that changes in mRNA levels "generally correlate" with changes in the level of the encoded protein does not appear to be supported by the evidence of record. In

fact, if the claimed invention is asserted to useful as a cancer diagnostic, the art of Meric et al. would be especially relevant and ***no*** conclusions can be made as to the protein expression levels in the tumor tissue compared to normal tissue based *solely* on the mRNA information given in specification.

Applicants argue (pages 19-21) that like Haynes, Chen examined only global relationships between gene and protein expression levels instead of for individual genes. "Chen merely selected proteins whose identity could be determined regardless of any changes in expression level." Also, "Chen did not distinguish between cancer and normal samples in their analysis." Finally, Applicant argues that as supported by Figures 2A-2C of Chen large mRNA level changes do correspond to protein level changes. The argument has been fully considered, but is not persuasive. Chen et al. focused on those mRNAs which encoded proteins that were detectable on 2D gel (page 308, col. 2). The method was sensitive enough to determine that proteins having different isoforms also often had different protein/mRNA correlation coefficients (page 309, paragraph bridging col. 1-2). It was concluded that absolute protein level did not influence the correlation with mRNA (page 310, col. 1). The results of Chen led to the conclusion that post-translation modifications are likely to affect the correspondence (or lack thereof) of mRNA to protein levels (see Discussion). Further it was shown (page 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression

levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. As to Applicants' argument that Chen did not distinguish between cancer and normal samples, it appears that the non-neoplastic lung samples were mapped with those of lung tumors (Fig. 2). While the purpose of the paper was not to distinguish tumor from normal sample, it clearly answered the question posed: Does mRNA expression correlate with protein expression in lung tumor samples? The answer was 'no' in a majority of cases. This result directly impacts the instant invention's use because it supports the Examiner's finding that the art does not sustain a reasonable expectation that for any particular mRNA expressed in tumor, the amount of protein and encoding mRNA will correlate or that changes seen in mRNA levels will convey as similar changes in protein levels from normal tissue to tumor tissue. As to Figures 2A-2C of Chen, these are correlations for only three particular genes: Op18, Annexin IV, and GAPD in 76 different lung cancer samples and nine normal lung samples. Further examining the mRNA/protein correlation of those three genes, it was determined that, "Even for the 28 protein spots (Fig. 2D) that were found to have a statistically significant correlation between their mRNA and protein, use of the average value resulted in a correlation coefficient value of –0.035, which was not significant (Fig. 3B)," (sentence bridging pages 309-310). Also, on page 309, first full sentence, Chen et al. state, "Among the 69 genes for which only a single protein spot was known (Table I), nine genes (9/69, 13%) were observed to show

a statistically significant relationship between protein and mRNA abundance..." Table I considered significance at $p<0.05$. These findings of Chen do not take away from that which Chen is relied upon for teaching, namely that assumptions cannot be made concerning mRNA/protein correlation with a reasonably certainty.

Applicant argues (middle of page. 21) that Chen cites Celis et al. (FEBS Lett., 480 :2-16, 2000) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved abundant proteins using a proteomic and microarray study of bladder cancer." The argument has been fully considered, but is not persuasive. This citation from Celis is actually a description in Celis of work by Orntoft et al. from a manuscript in progress (see p. 13, col. 1, third full paragraph of Celis). Celis provides a very limited and selective description of the work of Orntoft. It appears the work was finally published in Mol. Cell Proteomics 1:37-45,. In that article, Orntoft et al. studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts and that there was a general correlation between mRNA and protein alterations. However, Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region (see for example, page 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do

not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding mRNA instead of amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO300 in the instant specification. That is, it is not clear whether or not PRO300 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, there is little if any relevance of Orntoft et al. to the instant application.

Applicant again argues at page 21 that "the working hypothesis among those skilled in the art ... is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene" (emphasis omitted). Applicant's argument has been considered, but is not persuasive. The art cited in the instant application provides strong evidence that the "working hypothesis" of Applicant is incorrect (see arguments presented above).

Applicant argues (pages 21-23) that Fessler et al. shows that in 5/6 cases for which change in mRNA levels was reported, the change corresponded to change in protein level. Also, nothing in the results of Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in level of the encoded protein, thus supporting Applicant's assertions. For 6 samples in Table VIII of Fessler, mRNA was "absent" so that correlation with protein is not applicable. Applicant states that, "Nothing in these results by Fessler suggest that a change in the level of mRNA

for a particular protein does not generally lead to a corresponding change in the level of the encoded protein." The argument has been fully considered, but is not persuasive. As noted by Applicant (second paragraph, page 22 of response), "Of 13 up-regulated proteins, a change in mRNA levels is reported in only 3 such proteins. For these 3, mRNA levels were increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels are also decreased." Also, of the 13 up-regulated proteins, 5 corresponding mRNAs were unchanged and 5 were not detected ("absent"). That means, disregarding the undetectable mRNAs, that for 8 up-regulated proteins, only 2/13 showed corresponding upregulation in mRNA levels. The odds were slightly better for the 5 down-regulated proteins, with 3 corresponding mRNAs also down-regulated, 1 unchanged and 1 detectable ("absent"). So 3/5 down-regulated proteins showed corresponding down-regulation in mRNA levels. (See paragraph bridging cols. 1-2 of page 31295 of Fessler for data.) One can hardly conclude that the results of Fessler support that the change in levels of particular encoding mRNAs generally leads to a corresponding change in levels of the proteins. Indeed, what the results of Fessler et al. show is that a change in mRNA level does not necessarily have a corresponding change in protein levels and *vice versa*. This supports the high unpredictability for correspondence of protein and mRNA levels. When the findings of Fessler et al. are viewed with the findings of others such as Hayes et al. (previously cited) in the relatively new field of proteomics, the "...art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID

NO:11 positively correlates with the expression of the protein of SEQ ID NO:12". The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma.

Applicant argues (page 23-24) that Fessler et al. acknowledges many limitations of the reported experiments and that for some genes "transcript levels did not coincide well with corresponding protein levels, leaving it uncertain the extent to which actual changes in protein levels differed from mRNA levels when neutrophils were exposed to LPS." The argument has been fully considered, but is not persuasive. Fessler et al. attempted to avoid the problems associated with lowered sensitivity of their technique, by using only those spots which were common to all twelve pH3.0-10.0 two-D gels and which met statistical significance criteria (page 31301 end of first full paragraph). They also say that "By selecting for LPS effects common to all donors, we may not have characterized the range of genomic and proteomic heterogeneity present in the population and thereby may have focused on only a narrow portion of a broader biological response to LPS." This suggests that the discrepancy between mRNA and protein levels may be even larger than shown in the instant reference. The findings in general show that post-transcriptional and -translational modifications play an important role in biological influence of the encoding nucleic acid and encoded protein (*e.g.*, page 31301, middle of last paragraph). The reference does represent influential art and reinforces the complexity of translational factors

to be considered and supports the warning concerning the inability to draw conclusions about protein levels based on mRNA levels.

Applicant argues (page 24) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) are not surprising and provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. As Applicant has pointed out, it was stated in the previous Office action that while there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of page 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant. While Hu's finding that low expression levels do not necessary correlate with a biologically meaningful role of the gene in cancer does *not* mean that the gene cannot be used diagnostically for cancer detection. *However*, the gene must be enabled for diagnostic use, which it is maintained neither the encoding nucleic acids or polypeptide are enabled. Further, not knowing how the polypeptide expression level correlates with its mRNA levels, and not having a reasonable expectation that the levels of protein expression of the encoded polypeptide would be sufficiently different in lung tumor *vs.* normal tissue leaves the antibody which binds the encoded polypeptide without utility.

Applicant argues (pages 25-26) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection, citing the caveat of Example 12 of the Revised Interim Utility Guidelines. The argument has been fully considered, but is not persuasive. As stated in the previous Office action (page 18), it is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically regardless of function. Further, the instant claims are directed to antibodies and not the gene; therefore, the encoded protein must have diagnostic utility for the claimed antibodies to have diagnostic utility. For reasons discussed here and in the previous Office action, it is maintained that the protein does not have such utility.

Applicant argues (page 26) that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies and methods of using the antibodies. Applicant is reminded that each application is examined on its own merits. The patents which are referenced are not directed to the claimed invention of the instant application. The Examiner is not permitted to comment on the prosecution of other applications.

Applicant argues (page 26) that

> the position of the Examiner is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2701.01 [should be 2107.1]... Here, the mere identification of altered expression in tumors is relevant to the diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

Applicant's argument has been carefully considered, but is not persuasive. In the instant application, there is no demonstration of altered expression of the encoded protein in tumors. The art of record provides evidence that mRNA expression levels are not predictive of protein expression levels, therefore, further experimentation is necessary to determine if the claimed antibodies would be useful in a diagnostic manner as asserted in the instant specification. Furthermore, altered expression which is reported in Example 18 is not considered sufficient to support a specific and substantial or well-established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. As discussed previously and above, there is critical information lacking such that the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention. The cases discussed in this section of the MPEP are distinct from the instant situation. See the previous Office action dealing with *Cross.* In *Nelson v. Bowler,* the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. In this instance, pharmacological activity is not the same as altered gene expression. In *Nelson,* the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (page 885). "Here, however, a correlation between test results and pharmacological activities has been established." (page 886) Unlike in *Nelson,* the instant application does not have a showing of practical utility

because the specification does not allow the skilled artisan to use the instant invention for the reasons previously discussed. In *In re Jolles* (CCPA 1980), finding of utility was based on the close structural relationship to a prior art compound known to possess therapeutic utility. PRO300 has no known relationship. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:12 or the antibody which binds it nor established its utility as a cancer diagnostic.

Applicant argues on pages 26-28 that the Examiner has not met the initial burden of refuting that is more likely than not the claimed polypeptide does not have the asserted utility and that the Examiner has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and can be used as a diagnostic tool. The argument has been fully considered, but is not persuasive. Applicant is referred to the previous Office and discussions addressing Applicant's arguments above. One should not confuse credibility with specific and substantial use or enablement. The Examiner maintains that as a whole, the prior art does not provide a reasonable expectation that the level of expression of the nucleic acid of SEQ ID NO:11 positively correlates with the level of expression of the protein of SEQ ID NO:12. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. Protein levels do not need to be "accurately" predicated, but relative or absolute levels or information about

repeatability are critical for the skilled artisan to be able to use the instant invention without having to do further significant research. While absolute values are not necessary, certain criteria must be met for relative levels to be meaning for in terms of utility. Some criteria are what the relative difference is (*e.g.*, 0.5 times more or 10 times more expression), repeatability (*e.g.,* how may different lung tumor samples were used), whether the claimed polypeptide is overexpressed in the tissues in which that the PRO300 polynucleotide is overexpressed and comparison to the tissue matched control.

At page 27 Applicant *reminds* the Examiner that the MPEP cautions that rejections for lack of utility are rarely sustained by federal courts (MPEP 2107.02 III B.). Applicant's statements are noted, however, this section of the MPEP is directed to "When Is an Asserted Utility Not Credible?". Credibility has never been questioned in the instant application, therefore this argument is not applicable to the instant fact situation.

Applicant again argues (page 28) that the claimed invention has a specific utility as a cancer diagnostic tool, particular for lung cancer. The argument has been fully considered, but is not persuasive. While it is agreed that the asserted utility for the polynucleotide of SEQ ID NO:11 would be considered specific, although not substantial for the reasons of record, it is not agreed that the polypeptide of SEQ ID NO:12 does. The reasons for this have been discussed at length above, but include the lack of information regarding the presence or absence of the encoded PRO300 protein in tumor tissue compared to normal tissue, the lack of information about particular tumor type (*e.g.*, adenocarcinoma

versus squamal) the encoded protein may be expressed in, the lack of information about repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and the unpredictability of correlation mRNA and protein expression levels, it is maintained that the claimed invention is not supported by a substantial or specific utility nor is it enabled.

Applicant continues to argue the rejection at pages 29-30. These arguments have been carefully considered and addressed above. They are not found to be persuasive for the reasons provided above. Applicants argue on the page 30 that an invention only needs to be partially successful in achieving a useful result for utility (MPEP 2107.01). The argument has been fully considered, but is not persuasive. This passage from the MPEP refers to the issue of an "incredible" utility. That issue has not been raised by the examiner.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons of record.

Applicant asserts that the arguments regarding the utility of the claimed invention are sufficient to overcome the enablement rejection of the claims under 35 U.S.C. 112. However, since the submitted arguments were not persuasive to overcome the utility rejections under 35 U.S.C. 101, they are also not persuasive to overcome the instant rejection.

It would require significant further experimentation to be able to use the claimed antibodies because no definite function has been determined for the encoded protein, there is no definite function supported by the prior art, and there has been no correlation provided between the protein and any disease state. The specification does not provide sufficient guidance or working examples to be able to use the encoded polypeptide nor the antibodies that bind it diagnostically or therapeutically, for example in association lung tumors, without undue experimentation.

Claim Rejections - 35 USC § 102

Claims 1-5 stand rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/16318 for the reasons of record in the previous Office action.

Applicant argues (page 33) that they have made a proper claim of priority under 120 to obtain benefit of the WO 01/16318. However, benefit under 120 requires fulfillment of the requirements of 112, which includes a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. Since the instant specification does not meet the requirements of 35 U.S.C. 112, the instant application does not obtain benefit of

the earlier filed application. Since the earlier filed application was published more than 1 year before filing the instant application, it is proper art under 102(b).

Applicant argues that the data in Example 18 was first disclosed in PCT application PCT/US00/23328, and therefore, priority benefit should date back to this application. However, because of the reasons of record, the data in this example does not provide a specific, substantial and credible utility for the claimed invention, and therefore, the requirements of 35 U.S.C. 112, first paragraph are not met and benefit is not granted.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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